

PERSPECTIVE

Challenges in Clinical Trial Design for T Cell-Based Cancer Immunotherapy

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Chimeric antigen receptor T cells can induce impressive response rates in patients with refractory B cell malignancies. Adoptive transfer of tumor infiltrating lymphocytes or T cell receptor-engineered T cells are other promising treatment modalities currently in clinical development. Requirements for clinical trial design for T cell-based cancer immunotherapy significantly differ from established criteria for small-molecule or antibody-based anticancer drugs. Here, we highlight important differences regarding preclinical development, trial design, and reporting of clinical trials.

The development of cellular cancer immunotherapies is spurred by the success of anti-CD19 chimeric antigen receptor (CAR) T cells in B cell malignancies. These synthetic receptors, constituted by the antigen binding domain of an antibody fused to the T-cell receptor stimulatory and costimulatory domains, recapitulate a full-fledged T cell activation.¹ CAR T cells specific for CD19 have induced unprecedented response rates in refractory B cell-acute lymphatic leukemia and in diffuse large B cell lymphoma leading to approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Although CAR T cells are investigated in a large variety of hematological and solid

malignancies, the adoptive transfer of tumor infiltrating lymphocytes—which has been pursued for many years—or of T-cell receptor-engineered T cells are other promising treatment strategies (Figure 1).² The specificities for the clinical development of immune-oncology (IO) agents in general have been discussed previously.³ Universal challenges for clinical IO trials include a toxicity profile that is significantly different from conventional cytostatic cancer drugs regarding kinetics and dose-dependency, the need for new ways of response assessment, and ways to identify optimal combination partners.³ Early clinical trials for antibody-based IO agents mainly investigate one to two new agents alone or in

combination with the established standard (chemo)-therapy. Cellular cancer immunotherapy trials are more complex. In general, infusion of the cellular product is preceded by a lymphodepleting chemotherapy with its own potential for serious adverse events and is followed by the (per-protocol) application of rescue medication (e.g., steroids and tocilizumab) for cytokine release syndrome and other immune-related adverse events in a large proportion of patients (Figure 1). Additionally, the genetic engineering (e.g., generation of fourth generation CARs) and the manufacturing process (e.g., CD4 to CD8 ratio and activation protocols of T cells) of the cellular product itself often vary between different trials, which might have significant effects on efficacy and safety of the cellular product.

Safety considerations for early cellular cancer immunotherapy trials

For conventional cytotoxic drugs, one tenth of the lethal dose to 10% of mice has been established as starting dose for first-in-human clinical trials. This starting dose might be further reduced if toxicity occurs below this threshold in nonrodent animals.⁴ For molecular-targeted agents, such a clear convention is missing. The current practice of establishing the starting dose by a variety of toxicological parameters from experiments in at least one rodent and one nonrodent animal model seems to be safe.⁴ Minimal anticipated biological effect level was proposed as a starting dose for first-in-human studies with monoclonal antibodies by the EMA following the severe anti-CD28 antibody TGN1412 incident in 2007. Minimal anticipated biological effect level is not only based on *in vivo* but also on the available *in vitro* information.⁵

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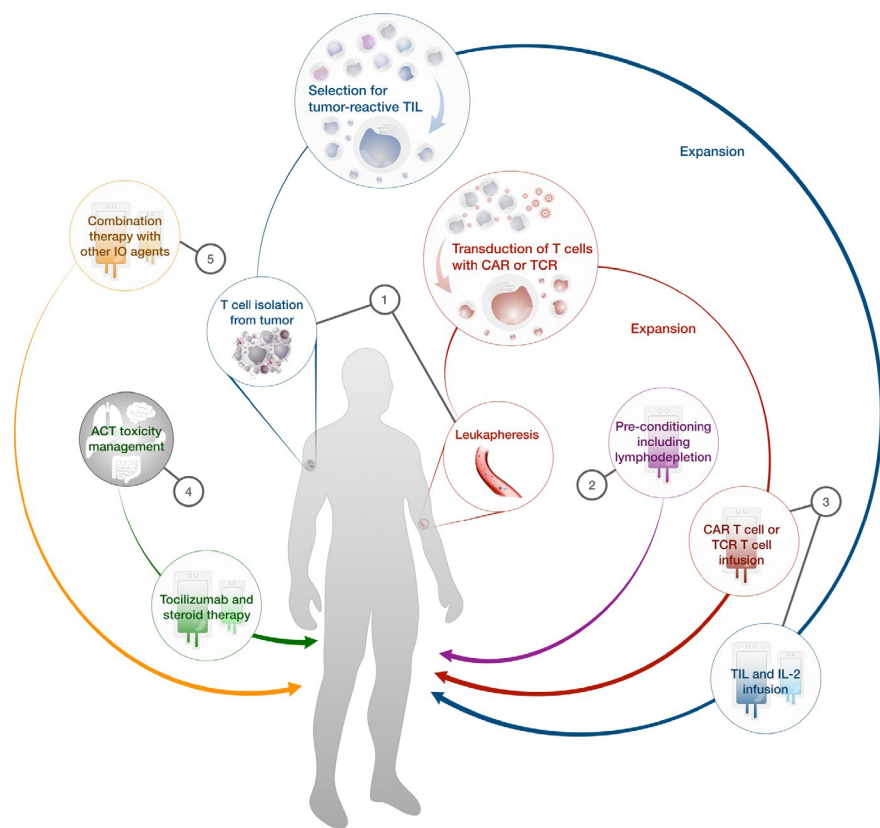


Figure 1 Adoptive T cell therapy. ACT, Adoptive T cell therapy; CAR, chimeric antigen receptor; IL-2, interleukin; IO, immune-oncology; TCR, T-cell receptor; TIL, tumor infiltrating lymphocyte.

For cellular immunotherapy, no recommendation on dose selection exists. Importantly, toxicity not only depends on the number of infused cells but is also influenced by the conditioning regimen and tumor burden of individual patients.³ Moreover, no appropriate animal model exists to predict *on-target* but *off-tumor* or *off-target* effects of T cell-based immunotherapy, resulting in several fatal incidents in early clinical trials for T cell-based therapies in colorectal cancer, melanoma, and myeloma.⁶ Risk mitigation strategies, such as split-dosing or application of a test dose, are also difficult to apply given the kinetics of T cell activation and expansion *in vivo* that usually climax around day 7. This was exemplified by a trial investigating the use of an affinity-enhanced T cell receptor (TCR) against HLA-A*01–restricted MAGE-A3. The first two treated patients within this clinical trial died from cardiac shock, secondary to cross-reactivity of the engineered TCR against an unrelated peptide on cardiomyocytes. The use of a split dose in one of the cases was not able to prevent this fatal event.⁶

A vigorous preclinical safety evaluation, including *in vitro* screening of human cells, tissues, and cellular models, as well as *in silico*-based approaches to exclude potential cross-reactivity, is therefore highly important. In addition, rather than focusing solely on a potentially safe starting dose, novel safety measures might be more important depending on the CAR or TCR construct under investigation. Safety measures currently under clinical investigation include the use of inducible suicide genes that can be pharmacologically activated upon appearance of higher grade toxicities (e.g., NCT02107963) or use of adapter CAR T cells as potential dose control of CAR T cell effector function.⁷ Other potential strategies include the clinical evaluation of new pharmacological rescue medications. One potential candidate could be dasatinib, which has recently been shown to potently and reversibly suppress CAR T cell cytotoxicity, cytokine secretion, and proliferation in NSG mice.⁸

Trial design and efficacy evaluation

In conventional clinical development programs, phase I trials were mainly designed

to establish safety, feasibility, and the recommended phase II dose. (Preliminary) efficacy was then evaluated in the subsequent phase II trial. As discussed above, side effects from CAR T cells or TCR-engineered T cells are often serious and might lead to fatal incidents. Decision on whether or not to further pursue the clinical development of such potentially harmful treatments highly depends on the relation between observed efficacy and toxicity. The classical phase I 3 + 3 dose escalation design is not suitable to continuously reassess this relation. More appropriate are adaptive, seamless phase I/II trials with multiple cohorts and constant reassessment of the ratio between efficacy and toxicity.⁹ Translating results from such trials to the general patient population is often difficult: expedited EMA (PRiority Medicines (PRIME)) and FDA (FDA breakthrough designation) approval for *axicabtagene ciloleucel* and *tisagenlecleucel* was based on data from single-arm phase I/II (ZUMA-1) or single-arm phase II trials (ELIANA and JULIET). As seen for many expedited approvals, efficacy was assessed by overall response rate (ORR) observed in treated patients without mature data on more patient-relevant end points, such as progression-free survival or overall survival. It is important to acknowledge the shortcomings of such trial designs in comparison to conventional drug approvals based on large phase III studies: First, because of the lack of a control arm, it remains unclear how much of the antitumor effect can be attributed to the conditioning chemotherapy and how much to the actual CAR T cell therapy. Especially, if the primary end point is ORR determined shortly after therapy (e.g., 3 months after infusion for the ELIANA trial). Furthermore, in the trials mentioned above, ORR is only reported for transfused patients. When interpreting these data, it has to be taken into account that a significant proportion of patients enrolled in those three clinical trials did not receive the planned CAR T cell infusion, for different reasons. In the JULIET trial, only 111 of 165 enrolled patients (67%) received a CAR T cell infusion compared with 101 of 111 in the ZUMA-1 trial (91%). Most frequent reasons for study dropout before CAR T cell infusion were disease progression, infections, other

adverse events, or death. Manufacturing problems only accounted for a small number of dropouts. Interestingly, the use of bridging therapies during the time interval for manufacturing and shipping of the final CAR T cell product was permitted in the JULIET but not in the ZUMA-1 trial. It could be speculated that this led to a difference in *a priori* patient selection (i.e., investigators might have been more reluctant to include patients with an aggressive tumor biology and a high risk for rapid progression to the ZUMA-1 trial). The observational end point “enrollment but no treatment” might be an important clinical indicator of real-world shortcomings of CAR T cell therapies. Future trials will need to incorporate careful scrutiny as to why a significant proportion of patients might not get treatment in spite of enrollment. It might be adequate for early trials that the logistics are not yet mature and efficient enough leading to a longer turnaround time with subsequent dropout (e.g., due to disease progression during waiting time). On the other hand, a high dropout rate even with optimized logistics in a highly selected clinical trial population might herald major problems in translating the results to a wider patient population.

Evidence development from cellular cancer immunotherapy trials

As mentioned above, protocols for cellular cancer immunotherapy are complex and can be modified in many ways. Currently, there are almost 600 registered clinical trials on CAR T cell therapy. About 50% of these trials focus on only three disease entities: acute lymphoblastic leukemia, B cell lymphoma, and multiple myeloma.² Given the fact that cellular immunotherapy trials can only be performed at highly specialized centers, many trials compete for a small number of patients. Moreover, treatment protocols and the cellular product itself largely differ in many cases. Together with the fact that many of the reported trials are small single-arm phase II studies, this significantly restrains sound evidence development for cellular cancer immunotherapy. Possible improvements

that have been proposed previously include standardized reporting schemes for clinical trials, creation of central repositories to report treatment and outcome in detail, as well as innovative models to summarize or “map” the currently available evidence in an efficient and rapid way.¹⁰

In addition, many of the trials on cellular cancer immunotherapy are performed as investigator-initiated clinical trials. It would be highly desirable to organize and structure these individual research efforts in clinical study groups to advance evidence development for cellular cancer immunotherapy in a more efficient way. One positive example is the European “EuroCARTForce” initiative that aims to jointly harmonize and improve management of adverse effects from T cell-based immunotherapy.

In summary, with T cell-based therapy having entered the clinical realm, immense efforts are being made to broaden its application and scope. With a growing number of trials but limited evidence for ideal and comparable trial design, there is a need for both investigators and sponsors to harmonize means. Aside from the trials themselves, there is also a critical need to render comparable the preclinical setting on product generation, efficacy, and safety testing as well as the regimens for preconditioning of patients. Together, these endeavors might culminate in faster development and prioritization of cellular products to the benefit of patients with cancer.

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CONFLICT OF INTEREST

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